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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/255,397	02/22/99	SERBEDZIJA G	18852-000500

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EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
1632	8

DATE MAILED: 01/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/255,397	Serbedzija et al
Examiner	**Group Art Unit**
Ram Shukla	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21 and 43* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21 and 43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5-7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-21 and 43 are pending in the instant application.

2. The instant application claims priority over US provisional applications 60/075,783 filed 02-22-98 and 60/100,950 filed 9-18-98.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claim 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Zikria et al (US 5,565,187, 10-15-96).

Claim 43 recites a method of testing toxicity of agents using a teleost wherein the agent is administered in vivo to the teleost and the response is determined by measuring the response in at least one tissue or organ of the teleost.

Zikria et al teach methods for studying capillary circulation using fish fry and tadpoles wherein the toxic agent is injected into the yolk sac and the capillary circulation is observed (see the abstract and claims 1, 5, and 7).

Therefore, the invention of claim 43 is anticipated by Zikria et al.

5. Claim 21 is rejected under 35 U.S.C. 102(e) as being anticipated by Yager(US 5,932,418, 8-3-99, filing date 4-4-97, priority date 4-8-96).

Claim 21 recites a method of screening an agent for its effect on cell death activity using a teleost wherein the agent is administered to a teleost and the response in detected in its tissues or organs.

Yager teaches a fish embryo screening test for genotoxic agents, including those which cause apoptosis (see columns 11, lines 3-67 continued in lines 1-41 in column 12, lines 1-33 in column 13, lines 15-34 in col 14, also see examples and claims).

Therefore, the method of claim 21 is anticipated by Yager et al.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stainier et al (Stainier DYR et al. Trends in Cardiovas. Medicine 4:207-212, 1994) in view of Driever et al (Driever et al Trends in Genetics. 10: 152-159, 1994), Weinstein et al (Weinstein BM et al. Nature Medicine 1:1143-1147, 1995), and Ozato et al (Ozato K et al. Cell Differentiation 19:237-244, 1986).

Claims 1-11 are drawn to a method for screening of an agent that increases or decreases angiogenesis using teleost wherein the agent is administered to the teleost and the response is detected by monitoring the change in angiogenesis or blood vessel formation. Dependent claims limit the type of change and stage of development of the teleost, different species of teleost and wild type or mutant strains of the teleost.

Claims 12-20 further limit the invention of the claim 1 by reciting a transgenic fish and that the agent is: administered in growth media or in a carrier that can be lipid, solvent or peptide; a compound or a library of compound, that the agent is a nucleic acid (DNA or RNA), a peptide, a protein, glycoprotein, carbohydrate, lipid or glycolipid); and injected into the teleost. Claim 20 recites that the blood vessels are visualized by microscopic analysis after alkaline phosphatase staining.

Stainier et al teach that zebrafish can be used as a model system to study cardiovascular development because it presents unique embryological attributes and is amenable to saturation style mutagenesis and because the embryo can be continuously observed and manipulated at all stages of development. Furthermore, because the embryo is transparent, the developing heart and vessels can be resolved at the single cell level. They further add that further understanding of the development of the cardiovascular system is important because it should lead to novel, differentiation-based strategies for the analysis and therapy of the disease state (see abstract). Furthermore, zebrafish heart development (initial heart tube stage) closely resembles the human heart (see col 1 on page 208 and figure 3). Additionally, the transparency of the zebrafish embryo and its continued accessibility at all stages of development, make it a very attractive system to screen for mutations affecting embryonic development and several mutagenesis strategies, such as irradiation and chemical mutagen treatment have been used to produce mutant zebrafish and for identifying genes (col 2 and 3 on page 210 continued on page 211 in col 1 and 2).

Driever et al review the state of art for the use of Zebrafish as genetic tool for studying vertebrate development. They teach that zebrafish can be used in genetic screens wherein the embryos are treated with mutating agents and organogenesis is studied and thereby genes responsible for organ development and function can be studied. Driever et al also review the injection of DNA, plasmid DNA or retroviral DNA and other types of introducing DNA in Zebrafish embryos and use of such transgenic fish in deciphering organogenesis, characterization of genes and their mechanism of function. This prior art also provides references for all these methods and their use. Finally, Driever et al conclude that the major strength of Zebrafish as a genetic system is that it permits the identification and functional analysis of new genes that control pattern formation and organogenesis. Zebrafish complement other experimental systems, since information gained from analysis in zebrafish can be extended to homologous systems in mice and other organisms (see entire article).

Weinstein et al teach the localization and function of a gene that generates vascular patterning. They also teach methods and provide references for the methods that are used for mutating fish using ethyl nitrosourea, monitoring of the changes in the vascular system

development of wild type and mutant embryos. Weinstein et al also teach methods of injecting material in the embryos in a protein carrier solution (see methods section).

Ozato et al teach production of transgenic fish by injecting plasmid DNA present in a carrier solution (EDTA containing buffer) in the oocytes of medaka embryos. They also teach methods for monitoring the presence of DNA and RNA and protein in different tissues of the transgenic fish (see methods section and figure 5).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the methods taught by Stainier et al, Weinstein et al or Ozato et al or by references provided in these prior arts and of Driever et al and apply candidate agents to fish embryo, larvae or adults in their growth medium or inject them in the embryo or oocyte in suitable carriers such as lipid or protein or EDTA containing buffer, let these develop and use them for screening the activity of candidate agents that affect angiogenesis with reasonable expectation of success because all the methods are taught by these prior arts or they provide reference for such methods. An artisan would have been motivated to use these methods because Stainier et al and Driever et al teach that teleost or zebrafish, due to the transparency of their embryo and easily accessibility for observation, make it a very attractive system to screen for mutations and for further understanding of the development of the cardiovascular system (that would include angiogenesis) and organogenesis in general . Stainier et al further provide motivation for such screens by concluding that such system is important because it should lead to novel, differentiation-based strategies for the analysis and therapy of the disease state.

Regarding claims 7-9, it is further noted that Brachydanio rerio or Giant rerio or medaka or puffer fish represent different species of teleost and they all have been used in experiments, e.g. Stainier et al have used Brachydanio rerio whereas Weinstein et al have used Danio rerio. Likewise medaka embryos have also been used (see Ozato et al).

Regarding claim 20, it is noted that the embryos can be directly observed under microscope after mounting on slides and alkaline phosphatase staining is a routinely used technique in immunostaining protocols.

8. Therefore, the claimed inventions would have been *prima facie* to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

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